

A close-up photograph of a newborn baby wrapped in a white, textured cloth. The baby's face is partially visible, showing their eye and forehead. The background is dark and out of focus.

# **MODULE 10: PHARMACOVIGILANCE**

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# 1. INTRODUCTION

This section introduces the concepts of pharmacovigilance and adverse drug reactions, discusses the burden of adverse drug reactions for children and explains the importance of pharmacovigilance in the context of antiretroviral therapy (ART).

## 1.1 Defining pharmacovigilance

WHO defines pharmacovigilance as the “science and activities related to the detection, assessment, understanding and prevention of adverse effects or any other possible drug-related problem” (1). It focuses on investigating and monitoring adverse drug reactions after medicinal products are licensed (2). Adverse drug reactions are a response that is noxious and unintended and that occurs at doses normally used in humans for the prophylaxis, diagnosis or therapy of disease or for modifying physiological function (2). They may vary in presentation and occurrence and are commonly divided into type A (augmented pharmaceutical response) and type B (bizarre or hypersensitivity) adverse drug reactions (3).

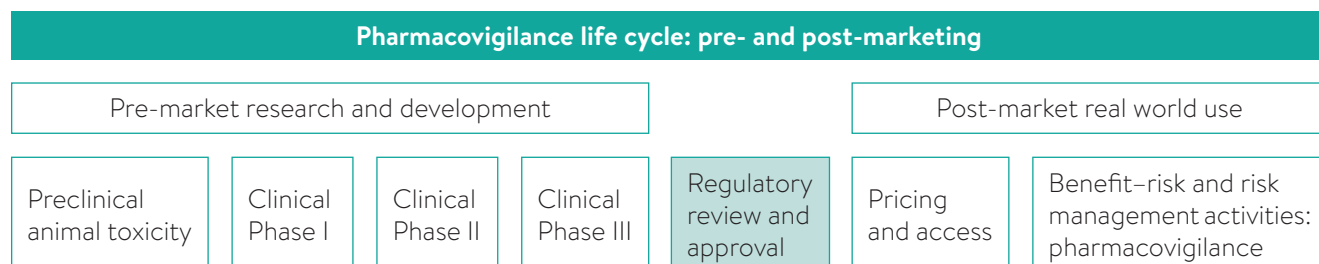
An example of a type A reaction in relation to antiretroviral (ARV) drugs for treating HIV is the negative effect of tenofovir on bone mineral density, which may increase fracture risk (4). An example of a type B reaction is efavirenz-related hypersensitivity in the form of a skin rash with systemic symptoms (5).

The global system of pharmacovigilance was first developed following the thalidomide tragedy in the 1960s, where thalidomide was used to treat nausea in pregnancy, resulting in serious teratogenic events among infants exposed in utero (6). Ideally, pharmacovigilance systems take a life-cycle approach, focusing not only on the properties of the prescribed medicine but also on how it is formulated, dispensed and administered (7,8). This approach is a continuum throughout the process of drug development, from initial research and development activities to final consumer use and is commonly divided into two stages (Fig. 10.1):

- pre-marketing surveillance: adverse drug reactions from preclinical screening and Phase I, II and III clinical trials; and
- post-marketing surveillance: adverse drug reactions from the post-approval stage and throughout a drug’s market life.

Pre-marketing safety assessment is generally limited for children. This commonly results from few children enrolled in paediatric clinical trials and/or the long latency between exposure to the medicinal product and the onset of the reaction, and less common adverse reactions may therefore not be detectable during this phase. The amount of dedicated information on the safety of medicines for neonates, children and adolescents at the time of marketing authorization is therefore very limited, which poses even more reliance on proper pharmacovigilance in the post-marketing stage (9).

**Fig. 10.1.** Timeline of pharmacovigilance for a drug from development (pre-market) to post-marketing use



The module on trial design covers issues concerning efficacy and safety data from Phase I to III studies, including the implications of relatively short follow-up times in drug approval trials and restricted entry criteria into trials.

Post-marketing pharmacovigilance can be conducted through passive and active surveillance systems.

In passive surveillance, health-care professionals or patients send spontaneous reports describing an adverse drug reaction after one or more medicinal products are administered to the marketing authorization holder or regulatory authority. Sometimes such first case reports are published, which may stimulate subsequent reporting. An example is the case report of efavirenz-induced gynaecomastia in a prepubertal girl with HIV, published in 2013 (10). A case series is a series of such reported cases, and these can help to generate hypotheses about an association between drug exposure and an outcome. An example is the case series of gynaecomastia cases reported to the National HIV & Tuberculosis Health Care Worker Hotline in South Africa and published in 2016 (11).

Active surveillance involves enhanced or targeted monitoring for certain events or drugs and seeks to ascertain completely the number of adverse drug reactions through a pre-planned process. Active surveillance is also commonly known as toxicity monitoring (such as the WHO ARV programme) or safety monitoring (12). An example is a cohort study that evaluated the prescribing of, adherence to and adverse drug reactions associated with ART in a large programme in Lagos, Nigeria (13).

Pharmacovigilance (passive or active) was not specific to drugs for children until the beginning of the new millennium, when the Pediatric Rule (United States) and the Paediatric Regulation (European Union) were implemented (14). Aspects related to children are now integrated early in the process of developing a new drug (pre-marketing). Stronger enforcement of requirements to obtain safety information for

children by regulatory agencies in recent years has resulted in an increased number of trials involving children. Following the Paediatric Regulation in Europe, the European Medicines Agency (EMA) issued the Guideline on the Conduct of Pharmacovigilance for Medicines Used in the Paediatric Population, which was recently updated (15).

## 1.2 Burden of adverse drug reactions among children and available studies

Age-specific pharmacovigilance is required among children, since they differ from adults because of ongoing neurobehavioural development and physical growth, including internal organ maturation (9). Further, different maturation milestones are likely to alter the susceptibility of children at different ages to specific adverse reactions and how they react to them, from (pre)term neonates to toddlers at one end of the spectrum to postpubertal adolescents at the other.

Factors influencing the susceptibility of children to adverse reactions for a given medicine include:

- changes in the maturation of organ systems (such as skin, airways, kidney, liver, gastrointestinal system, brain and blood-brain barrier as well as drug transporters) during growth and their development (ontogeny) leading to a different pharmacodynamic and pharmacokinetic profile of a medicine to what is known in adults;
- rapid changes in body mass and shape that can reduce the therapeutic window, leading to increased susceptibility to dose-related adverse drug reactions;
- the immaturity of many organ systems that might lead to different vulnerability to adverse drug reactions in some subpopulations of children, such as preterm neonates;
- the presence of specific pharmaceutically active excipients that may have unintended effects for children (such as alcohol), leading to a risk of adverse reactions; and

- the impact of short- and long-term effects on the developing organs and organ systems, such as the nervous system, skeletal growth and sexual maturation; such effects may only become obvious, visible or identifiable in the long term, with remarkable delay, in adolescence or adulthood.

These considerations highlight the importance of taking into account aspects related to organ maturation and developmental pharmacology when performing pharmacovigilance activities for children and imply that the value of long-term follow-up should be considered systematically (16).

A recent meta-analysis of the incidence of adverse drug reactions in paediatric observational studies demonstrated that the rates of all adverse drug reactions that resulted in hospital admission ranged from 1% to 10% among children (pooled estimate 3%). For hospitalized children, these rates were higher, ranging from 1% to 17% among children exposed to a drug (17). Anti-infective drugs (including ARV drugs) and anticonvulsants were the most frequently reported therapeutic classes associated with adverse drug reactions among hospitalized children.

Although the evidence is limited, the burden of adverse drug reactions among children appears to be similar in high-income countries and low- and middle-income countries (5). Besides the impact of adverse drug reactions on morbidity and mortality and the associated direct costs of managing them, adverse drug reactions also have other significant costs in terms of the loss of confidence in the health system, financial losses of the pharmaceutical industry, increased non-adherence to treatment and the development of drug resistance to anti-infective drugs (18).

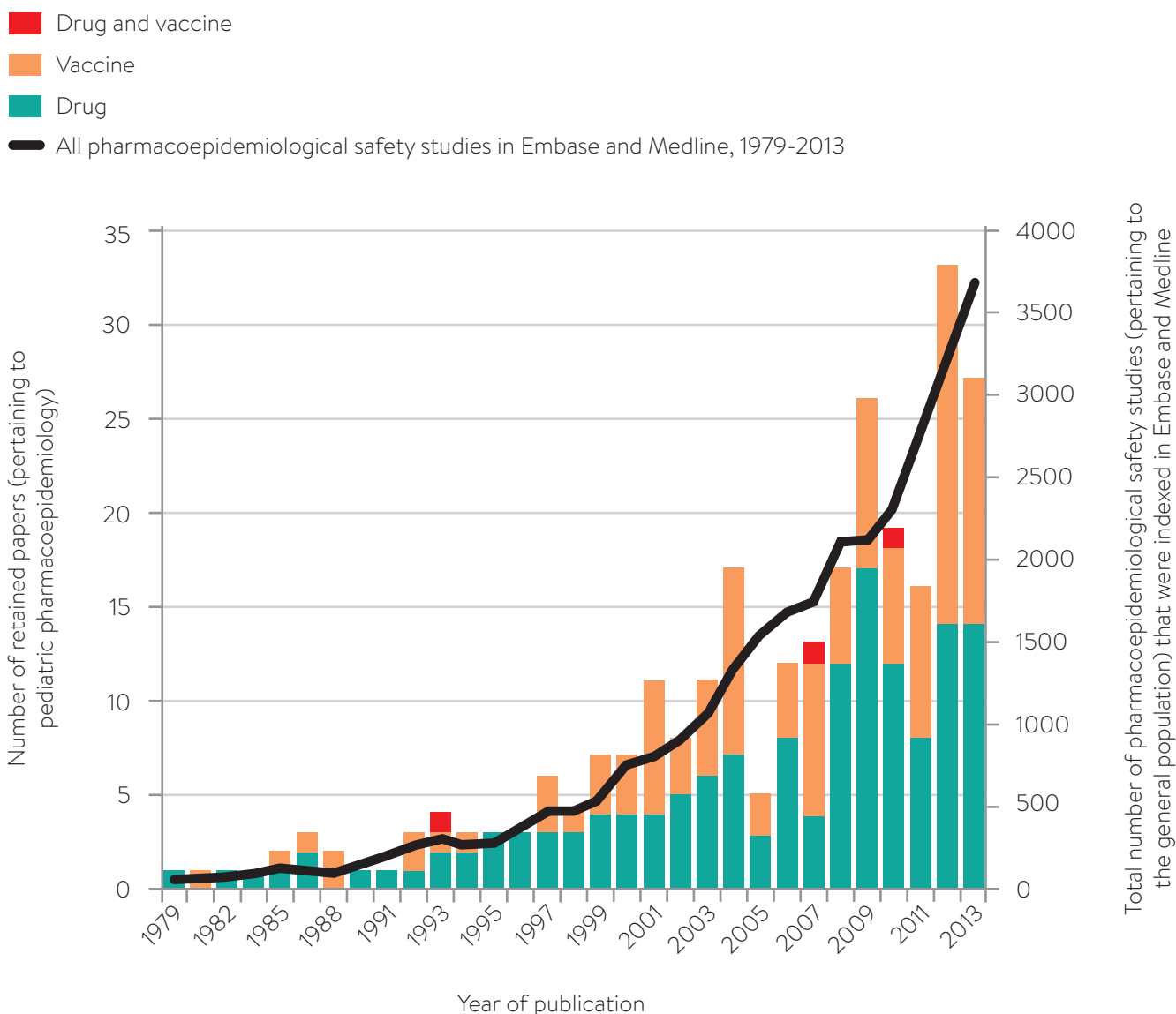
Another systematic review focused on studies quantifying the association between drug exposure and adverse drug reactions among children and adolescents younger than 18 years (19). Surprisingly, only 268 relevant articles were retrieved, with an increase in the number

published over time, as Fig. 10.2 demonstrates. Rather concerning was the great disparity between the number of studies involving children compared with adults, as represented in the right vertical axis of Fig. 10.2, showing about 25–30 published studies involving children versus about 3500 studies involving adults per year in recent years. The following section explores some of the challenges related to conducting pharmacoepidemiological studies involving children exposed to and living with HIV, and this helps to understand the causes of the low level of evidence for adverse drug reactions among children.

For children exposed to HIV and children living with HIV, ART provides enormous benefits, including dramatically reduced mortality risk, improved growth, immune recovery and viral suppression and improved cognitive development (20). However, similar to any drug, ARV drugs have been associated with adverse drug reactions. Short-term adverse drug reactions after initiating ART may include dizziness and gastrointestinal disorders as well as cognitive and sleep disorders. Longer-term adverse drug reactions associated with ARV drugs include changes in body fat distribution (lipodystrophy) and negative effects on bone health (20).

In some studies of ARV drugs, the rates of ART discontinuation have been higher in post-marketing observational studies than in the clinical trials that led to regulatory approval. For example, for dolutegravir (DTG), about 10% of adults in a large cohort study discontinued DTG during the first year of treatment versus only 2–4% of adults in regulatory clinical trials (21). In addition, data on the efficacy of specific combinations of ARV drugs from Phase I to III studies may be limited to specific populations and/or have smaller sample sizes, limiting the ability to evaluate adverse drug reactions. These challenges highlight the ongoing need for long-term pharmacovigilance of ART across different populations of HIV-exposed children and children living with HIV to ensure that the drugs are safe and effective.

**Fig. 10.2.** Number of pharmacoepidemiological safety studies involving children



Source: Osokogu et al. (19). © 2016 The Authors. Pharmacoepidemiology and Drug Safety, published by John Wiley & Sons Ltd.

### 1.3 Importance of pharmacovigilance in the era of expanded access to ART

Post-marketing pharmacovigilance is essential to monitor the longer-term safety of drugs, especially in specific populations and/or situations that are not normally included in pre-marketing studies. Underlying this is the importance of appropriately collecting and reporting safety data to provide information for clinical decision-making. The expansion of

two key public health programmes has resulted in substantial exposure of fetuses in utero and children to ARV drugs: initiatives to prevent the perinatal transmission of HIV and initiatives to improve the survival of children with HIV.

#### Initiatives to prevent the perinatal transmission of HIV

Current WHO and national guidelines recommend that all pregnant women living with HIV receive lifelong ART to prevent the perinatal transmission

of HIV and to improve maternal health. Global coverage of ART for preventing perinatal transmission and maternal HIV treatment is high, with UNAIDS estimating that coverage of ART among pregnant women living with HIV was 76% in 2016 (22). Consequently, HIV transmission rates are now less than 1% in many high-income countries and less than 5% in several low- and middle-income countries (23,24), and estimates suggest that 2 million children avoided acquiring HIV infection globally from 2000 to 2015 because of the roll-out of ART for pregnant women (25).

With the successful scale-up of maternal ART, an estimated more than 1 million infants are exposed to ART in utero and/or in early life through short-term prophylactic ART (26). Although ART is highly effective in reducing perinatal transmission, and preventing children from become newly infected is unquestionably beneficial, there is also global recognition of the potential negative impact of exposure to ART during fetal and postpartum growth and development on the morbidity, mortality and developmental outcomes for millions of children (26,27).

In addition, the roll-out and scaling up of ARV drug pre-exposure prophylaxis to pregnant and breastfeeding HIV-negative women will result in ongoing exposure to these drugs among their offspring, in utero and during breastfeeding, further increasing the number of children exposed to ART globally. The current size of the HIV-uninfected population exposed to pre-exposure prophylaxis is likely to be relatively small, since in many countries pre-exposure prophylaxis is only available to key populations at higher risk such as men who have sex with men and sex workers but this population may be substantially larger in the future.

To sustain the uptake of these programmes and to reduce uncertainty around safety issues related to ARV drugs, post-marketing surveillance of pregnant women exposed to ART is of utmost importance. This is because no ARV drugs have been categorized as United States Food and Drug Administration (FDA) category A in pregnancy, indicating that adequate and

well controlled studies of pregnant women have failed to demonstrate a risk to the fetus in the first trimester of pregnancy (and no evidence exists of risk in later trimesters). This FDA classification system has now been replaced with more informative labelling to enable the health-care provider and patient to better assess risk, although all ARV drugs classified while the system was in use were category B or lower, demonstrating the moral duty to collect adequate safety data (28).

### **Initiatives to improve the survival of children with HIV**

Children living with HIV, who may or may not have been exposed to ART in utero and/or during breastfeeding, and who are prescribed lifelong ART, need proper monitoring to assess the short-term and longer-term effects of ART. ARV drugs have greatly improved the survival of children living with HIV in high-income countries and low- and middle-income countries, even though coverage among children continued to lag behind that among adults, at 43% versus 53%, respectively, in 2016 (29). Children living with HIV are exposed to lifelong ART throughout critical developmental stages of childhood, including the metabolic and hormonal changes of puberty during adolescence. UNAIDS estimates that, in 2016, 2.1 million children younger than 15 years were living with HIV globally, and 160 000 children were newly infected, with projections suggesting that the number of children acquiring HIV will only decline to 100 000 by 2020 (25).

## 2. CHALLENGES

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This section discusses the challenges of conducting pharmacovigilance of ART among children in low- and middle-income countries.

### 2.1 General pharmacovigilance challenges

This subsection describes the challenges relevant to the safety of all medicine, and the next subsection describes those specific to ART.

#### 2.1.1 Regulatory challenges in low- and middle-income countries

There have been significant advances in pharmacovigilance activities in recent decades, and systems are considered well established in most high-income countries. Regulatory developments have supported these advances, and the absolute number of paediatric safety studies has increased since the introduction of the Best Pharmaceuticals for Children Act in the United States in 2002 and the Paediatric Regulation in the European Union in 2007 (19). The implementation of pharmacovigilance in low- and middle-income countries, however, is highly variable. Some countries have no systems at all, whereas a few have more established programmes that are comparable to those in high-income countries, such as South Africa (7). A review of the general pharmacovigilance systems of 46 countries in sub-Saharan Africa in 2010 concluded that the capacity for regulating health products was inadequate in sub-Saharan Africa (30).

Given the importance of pharmacovigilance among children and adults across all settings, WHO has defined the minimum requirements for any routine national pharmacovigilance system, focusing on the least resource-demanding passive surveillance methods that can be implemented without major investment (31). These requirements include:

- a national pharmacovigilance centre with designated staff and at least one full-time staff member;
- the existence of a national spontaneous adverse drug reaction reporting system, incorporating a national individual case safety report form (an adverse drug reaction reporting form);
- a national database or system for collating and managing adverse drug reaction reports; and
- a national pharmacovigilance advisory committee to provide technical assistance on causality assessment, risk assessment and management, case investigation and crisis management, including crisis communication.

Fortunately, the number of low- and middle-income countries conducting passive surveillance and reporting to the WHO Programme for International Drug Monitoring has steadily increased. For example, in a review of pharmacovigilance systems in sub-Saharan Africa, 72% of countries participated as an official or associate member of this Programme (30). However despite a rise in the number of spontaneous adverse drug reaction reports from low- and middle-income countries (7), very few countries have reached the desired target of 100 reports per million inhabitants. Reported challenges to improving the reporting of adverse drug reactions in low- and middle-income countries include (7):

- busy clinics, high patient volumes and few health-care professionals, with no time to focus on reporting suspected adverse drug reactions;
- health-care professionals being uncomfortable reporting adverse drug reactions because they fear perceptions of professional error or culpability, lack of clear legal provisions to guarantee confidentiality of submitted reports, lack of trust in the integrity of authorities and lack of proper training; and

- postal services and Internet being unreliable, complicating reporting to national centres (7).

The review highlighted several gaps in pharmacovigilance in sub-Saharan Africa (30). Although most (74%) of the 46 countries in sub-Saharan Africa had a national medicine regulatory authority and 78% had a national medicine policy, less than half (41%) had a national policy related to pharmacovigilance and medicine safety, and only one third (30%) had a legal mandate to monitor adverse drug reactions. Further, less than one third (28%) of the countries had legal provisions requiring marketing authorization holders to report all serious adverse drug reactions to the national medicine regulatory authority, and only 17% of countries required marketing authorization holders to conduct post-marketing pharmacovigilance.

On the positive side, most (74%) of the countries had a pharmacovigilance centre with a clear mandate and formal organizational structure, 39% had national pharmacovigilance guidelines and a safety advisory committee and 45% had a drug information service providing drug information to health-care professionals and the public.

Coordination among all stakeholders was, however, minimal – only 28% of countries had a platform or strategy to coordinate pharmacovigilance activities at the national level. A pharmacovigilance database existed in half (50%) the countries, but coordination and collation of pharmacovigilance data from all sources was inadequate. The review did not focus on pharmacovigilance involving children, which has only relatively recently gained attention in high-income countries.

### **2.1.2 Competing resource and capacity challenges**

Pharmacovigilance activities involving adults and children have historically been underdeveloped in low- and middle-income countries, partly because of some stakeholders perceive that the cost of pharmacovigilance infrastructure competes with the distribution of scarce resources for direct care delivery (32).

The priority in low- and middle-income countries in recent years has been to establish access to essential medicines to reduce morbidity and mortality. In this light, investing in pharmacovigilance systems was considered an unaffordable luxury (7), thus impeding the allocation of time and resources to developing sustainable global pharmacovigilance. This is especially true for HIV, with the rapid roll-out of ART through the Global Fund to Fight AIDS, Tuberculosis and Malaria and the United States President's Emergency Plan for AIDS Relief (PEPFAR) in early 2000 being aimed primarily at saving millions of lives. Consequently, access to essential medicines for treating such common health conditions as malaria, pneumonia, HIV and diabetes mellitus has increased substantially in low- and middle-income countries, and global coverage of ARV drugs for people living with HIV increased to 53% in 2016 (33).

The consequence of this success is an increasing number of people globally at risk of adverse drug reactions, especially in communities with limited education and fewer trained health-care professionals to guide the safe and appropriate use of medicines. Increased global medicine exposure, lack of information on drug safety and ongoing significant presence of comorbidities emphasize the need for efficient pharmacovigilance systems in low- and middle-income countries, especially for large-scale treatments such as ART and among vulnerable populations such as pregnant women and children.

### **2.2 Specific ART-related pharmacovigilance challenges**

Beyond general challenges to passive and active surveillance in low- and middle-income countries, several specific challenges exist for passive and active surveillance of ARV drugs. We first discuss challenges for case reports and subsequently the challenges for conducting retrospective and prospective epidemiological studies.



### **2.2.1 Challenge in assessing the causality of case reports**

The challenge in assessing causality for suspected adverse drug reactions from case reports is that they are rarely specific to the individual drug, diagnostic tests are usually absent, a re-challenge (such as reintroducing the drug to the patient after an adverse drug reaction) is rarely ethically and clinically justified, and there are frequently no denominators of patients at risk.

Assessing causality for ARV drugs is even more challenging, since multiple drugs are taken together in the form of fixed-dose combinations for ART or HIV prophylaxis, and many may produce similar adverse events. The presence of comorbidities and concomitant treatments (such as for tuberculosis or malaria) further complicate the assessment of causality.

In practice, few adverse drug reactions have a certain or unlikely relationship with a specific drug, and most are somewhere in between these extremes, such as possible or probable. Recognizing the presence of adverse drug reactions may also be more difficult since they may present with a different pattern or severity because of environmental or behavioural factors or comorbid conditions and concomitant medications. Higher incidence rates of drug–drug interactions and adverse drug reactions are therefore naturally expected in low- and middle-income countries (12).

In addition, late initiation of ART, frequently with advanced HIV disease and malnutrition, limited health-care provider expertise and drug stock-outs may result in treatment interruptions and restarts or drug substitutions, both for HIV and comorbidities, that can also contribute to higher rates of adverse drug reactions. Compared with the common comorbidities in low- and middle-income countries, providers in high-income countries face a different array of confounding health conditions and concomitant drugs used, such as illicit drugs, psychotropic drugs and lipid-lowering agents, which can also complicate pharmacovigilance activities.

### **2.2.2 Challenge to distinguish between adverse drug reactions and dosing errors**

The risk of medication dosing errors (under- or overdosing) is high for children and especially among young children receiving ARV drugs, who require frequent dose changes in response to rapidly changing body weight. Use of formulations for children, such as granules and sprinkles, liquids and small tablets, requires proper training and support of the caregiver by the skilled health-care worker and, if not implemented, may result in dosing errors causing adverse drug reactions and drug–drug interactions.

Case reports of medication dosing errors involving infants who received up to 10 times the recommended dose of zidovudine prophylaxis or treatment and the subsequent adverse events (34) highlight the risk for such errors and helped stakeholders advocate for appropriately sized administration vehicles such as syringes for children (35).

### **2.2.3 Challenge in generalizing results from high-income countries**

Currently, pharmacovigilance studies involving children originating from high-income countries dominate the field, but many high-income countries have relatively few children living with HIV compared with low- and middle-income countries. For example, the European Pregnancy and Paediatric HIV Cohort Collaboration has conducted post-authorization safety studies on behalf of pharmaceutical companies for the EMA. These studies involve secondary analyses of prospective cohort data, supplemented by questionnaires on outcomes specific to adverse drug reactions (36). Of the five ARV drugs with findings published to date (36–40), two were for drugs used relatively infrequently in Europe and correspondingly had sample sizes of less than 200 in each study, highlighting the challenges of conducting pharmacovigilance studies with small sample sizes (37,40).

The availability of newer ARV drugs differs by income setting. Children in low- and middle-

income countries are frequently prescribed generic first-generation individual ART drugs and generic fixed-dose combinations, which may no longer be considered preferred regimens in high-income countries. Thus, new evidence for the drug safety of older regimens will no longer be generated from high-income countries with well developed pharmacovigilance systems, leading to an even larger disparity in safety information between low- and middle-income countries and high-income countries.

#### **2.2.4 Challenges based on the quality of source data**

Retrospective epidemiological studies in low- and middle-income countries may rely on extracting data on the outcome and exposure from paper medical records, and the quality of these is likely to vary widely depending on the study context. Treatment records may be incomplete or missing and difficult to retrieve, and a lack of recorded viral load data in many low- and middle-income countries restricts the

ability to investigate the real-world adherence, effectiveness and safety of specific ARV drugs. Adverse drug reactions and medication use are often not documented because of lack of time and lack of awareness of their importance.

#### **2.2.5 Heterogeneity of exposure and populations: effect modification versus power**

Children with ART exposure are not a homogeneous group but comprise distinct populations of HIV-negative children and children living with HIV, all with ART drug exposure differing by duration and the combination of drugs given. These differences may all affect the rates of adverse drug reactions, and studies need to distinguish these factors and study safety by the type of regimen and population. Only if effect modification is absent may exposure be pooled. The need to evaluate effect modification affects the power. ART exposure should be well documented, including maternal and infant exposure, although this proves to be difficult even in high-income countries (41).

A good example is the West Cape Province of South Africa, which has an electronically linked health record system linking maternal and infant records, including pharmacy ART records with a range of health records, including hospital admissions, death and cancer registries. Such surveillance systems may provide a critical foundation for well powered pharmacovigilance systems.

#### **2.2.6 Challenges from selection bias and loss to follow-up**

The surviving and ageing perinatally infected children living with HIV make pharmacovigilance studies difficult to conduct. Challenges include how to select representative samples of children and the appropriate duration of follow-up. Because of dropout or loss to follow-up, the analysable amount of person-time may be low, limiting the power to investigate longer-term safety. This affects the confidence in the findings of different studies.



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### 2.2.7 Multiple outcomes of interest

Paediatric safety outcomes of interest range from prenatal, perinatal and neonatal to longer-term outcomes. Many outcomes may require diagnostics that are not generally available in clinics in low- and middle-income countries, such as dual-energy X-ray absorptiometry and neurological and psychiatric assessment. Longer-term outcomes of short-term and lifelong ART

exposure range from effects on physical growth to rare remote events such as malignancies in adulthood, and all need to be investigated. Studying such a broad range of health outcomes will require varied study design approaches and proper assessment of outcomes over a long lifespan, which is challenging because of the lack of automated and linked health records, migration and loss to follow-up.

## 3. SOLUTIONS

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The safety of ART has improved considerably over time but, similar to any active compounds, vigilance is required, especially in vulnerable populations (such as pregnant women, children and immunocompromised people). Solutions to improve pharmacovigilance in its broader context start with preventing or minimizing risks. Having data available to identify and minimize the risk requires comprehensive signal detection and evaluation studies being in place, to generate actionable information.

### 3.1 Minimizing the risks

Pharmaceutical adverse drug reactions (type A) may be prevented through an array of risk-minimizing activities such as:

- providing access to up-to-date information on the safety of ARV drugs in different populations to health-care providers in high-income countries and low- and middle-income countries so that well informed decisions can be made;
- pretreatment screening to identify people at high risk of specific adverse drug reactions;
- avoiding prescribing concomitant medicines with a shared risk for similar adverse drug reactions, such as multiple nephrotoxic agents;

- implementing medication review into the standard of care to identify the potential for drug–drug interactions; and
- training health-care providers and patients to promptly recognize, treat and document adverse drug reactions.

### 3.2 Improving the regulatory framework to create a safety culture

A key reason for the lack or limited implementation of pharmacovigilance in low- and middle-income countries is a lack of national regulations to enforce the responsibilities of the pharmaceutical industry, including generic drug manufacturers, regarding safety reporting of adverse drug reactions to national pharmacovigilance centres (18). With a pharmaceutical market in sub-Saharan Africa estimated to be worth US\$ 3.8 billion to 4.7 billion, the pharmaceutical industry, both innovator and generic, is a major stakeholder in pharmacovigilance activities. The industry should replicate the standard pharmacovigilance practices they undertake in high-income countries and implement similar activities in low- and middle-income countries to safeguard patients and protect the public health of the communities in which they market their products.

Generic drug manufacturers provide a significant proportion of ARV drugs for low- and middle-income countries, and the lower pricing ensures greater access to drugs among the affected populations. However, historically, generic drug companies may have devoted fewer resources for pharmacovigilance and may perceive that monitoring adverse drug reactions is not relevant for generic drugs with well known safety profiles (18). Generic drug manufacturers may not see it as their responsibility to support pharmacovigilance on market entry even when the innovator company is not marketing the compound. However, in the era when increasingly large proportions of the population living with or exposed to HIV globally are receiving generic ARV drugs, there are increasing calls for regional and national regulations and an increased role for the generic pharmaceutical industry to share the responsibility for pharmacovigilance with other global and national stakeholders.

### 3.3 Strengthening capacity

A 2010 review of existing pharmacovigilance systems in sub-Saharan Africa demonstrated that there was existing capacity in the WHO African Region to conduct medicine safety research that can help identify, evaluate and confirm medicine-related risks (30). Active surveillance, including Phase IV studies to evaluate the safety and effectiveness of medicines, had been or were being conducted by academic institutions, public health programmes, hospitals and international organizations in 22 African countries, although most studies were related to malaria treatment.

To improve the coordination of existing research capacity and resources, regional groups in Africa could be supported to develop networks that link research institutions and regulatory authorities to increase medicine research capacity.

Pharmacovigilance centres in sub-Saharan Africa could also collaborate on a more global level, since many training courses and opportunities for remote collaborations exist and are available remotely (see the section on useful resources).

Building and sustaining the required human capacity to identify adverse drug reaction signals and manage them requires introducing pharmacovigilance in undergraduate- and graduate-level teaching for all health professionals globally. The WHO Collaborating Centre for Pharmaceutical Policy and Regulation in Utrecht, Netherlands, which conducts academic research at the interface of pharmacoepidemiology and policy analysis, has been charged with developing such programmes (42).

The establishment of a WHO Collaborating Centre for Advocacy and Training in Pharmacovigilance in Accra, Ghana has been a major step towards consolidating the establishment of pharmacovigilance in Africa (7). Since 2009, this Centre has been providing pharmacovigilance training, building capacity, promoting advocacy and strengthening adverse drug reaction reporting, with a focus on passive surveillance, in African countries. WHO is also building capacity in sub-Saharan Africa through the Global Training Network on vaccine quality and the through the WHO Collaborating Centre for International Drug Monitoring in Uppsala, Sweden, with courses on adverse events following immunization (passive surveillance).

The Pharmaceutical Industry Association of South Africa organized pharmacovigilance training in South Africa with a focus on pre-marketing clinical safety research or post-marketing adverse events following immunizations. Courses and training on pharmacovigilance are also available from other academic institutions and centres of excellence (see the section on useful resources). Teaching institutions with centres of excellence within their own countries also conduct many active surveillance studies, providing the potential for mentorship to non-teaching hospitals to build the capacity of health-care workers in pharmacovigilance at the local level.

In the European Union, the Eu2P programme was developed through funding from the Innovative Medicines Initiative. It is currently offering innovative web-based education and training in

pharmacovigilance and pharmacoepidemiology, including master and PhD programmes that can be conducted alongside day-to-day work and are available for applicants from low-income countries, including regulatory staff and health-care workers. Internships are available in WHO collaborating centres in Uppsala (Sweden), Accra (Ghana), Utrecht (Netherlands) or Rabat (Morocco) (see the section on useful resources).

The pharmaceutical industry can assist national pharmacovigilance programmes by limiting their employment of national qualified personnel from pharmacovigilance centres and investing in pharmacovigilance training. To retain well trained personnel, salaries in the public sector may need to be increased to avoid a drain into the private sector. Joint PhD programmes with high-income countries and private companies may facilitate the retention of personnel in research settings.

### 3.4 Focus on active surveillance

In the presence or absence of functional passive surveillance systems, the primary focus should be on setting up active surveillance. One of the benefits of active surveillance over passive surveillance is the ability to generate information that may inform decision-making, since there is a higher probability of evaluating and quantifying the relationship between the adverse drug reaction and the related drug. Active surveillance may be implemented using existing capacity: for example, through demographic surveillance networks and public health programmes, which exist in many low- and middle-income countries. Collaboration can be initiated between pharmacovigilance experts and public health officials.

### 3.5 Pooling existing data from active surveillance studies

Merging or pooling data from multiple studies increases the statistical power of analysis and can be a relatively cost-efficient approach. Standardized data exchange protocols are available to aid data mergers, including the HIV Cohorts Data Exchange Protocol (43) and the International Epidemiology Databases to Evaluate AIDS Data Exchange Standard.

A recent example of a large-scale data merger is the Collaborative Initiative for Paediatric HIV Education and Research cohort collaboration, which has conducted a data merger on 93 351 children younger than 18 years across 12 HIV observational cohort networks globally to investigate the incidence and predictors of switching to second-line ART (44). Among other findings, children starting ART with non-nucleoside reverse-transcriptase inhibitor-based regimens have been found to have a higher incidence of switching compared with those starting with protease inhibitor-based regimens.

Such collaboration can be a key source of pharmacoepidemiology data, especially in settings with weak underlying pharmacovigilance systems. The existence of electronic health records comprises another available resource for pharmacoepidemiological pharmacovigilance safety studies (19).

### 3.6 Developing standardized methods and protocols

Using standard protocols and definitions for outcomes, exposure and confounders for active surveillance studies may increase validity and ease the pooling of data from disparate settings. Common data models for data collection may be created, facilitating pooling and the use of common analytical data scripts, especially in areas with limited capacity.

### 3.7 Pooling of spontaneous reporting data

A crucial aspect of pharmacovigilance is the ability to easily pool data from disparate sources to inform the global community of emerging trends in adverse drug reactions. National pharmacovigilance systems should establish and maintain adverse drug reaction databases that are compatible with the international standard format for adverse drug reaction reports, known as individual case safety reports. The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use developed this international standard, known as the ICH-E2b, which allows easy exchange of adverse drug reaction data between countries, regulatory authorities and the pharmaceutical industry.

Low- and middle-income countries can use the VigiFlow data management system from the WHO Collaborating Centre for International Drug Monitoring at low cost, in which the ICH-E2b is fully integrated. Further, international data sharing is necessary to support global pharmacovigilance, especially given international trade and traffic in pharmaceuticals, and specifically, the small numbers of specific adverse drug reactions involving children.

The power to detect adverse drug reaction signals is greatly enhanced when a data management system can receive and collate pharmacovigilance data from all sources, including routine adverse drug reaction monitoring integrated within public health ART programmes, clinical trials, immunization programmes, active surveillance and periodic safety updates from the pharmaceutical industry.

### 3.8 Harnessing WHO technical support

To support the safe introduction of new ARV drugs for children and address the gaps in safety data within national programmes, WHO provides technical support to countries to implement both routine toxicity monitoring via the HIV patient monitoring system and active adverse drug reaction surveillance for ART. WHO has developed and disseminated patient monitoring tools that capture and enable reporting of treatment limiting adverse drug reactions. WHO also supports the implementation and the strengthening of data quality to encourage the generation of reliable data and maximize the utility of collected data. WHO works with health ministries and technical partners to adapt the minimum datasets, tools and protocols to individual country settings and is supporting the implementation of surveillance of drug safety among pregnant women in Malawi and South Africa.

Moreover, WHO has developed an ARV drug toxicity monitoring tool that provides step by step instructions and reporting tools for countries to implement both routine monitoring of toxicity and active adverse drug reaction monitoring at selected sentinel sites for new ARV drugs among children. WHO aims to produce additional tools and annexes for new ARV drugs, including new ARV drug formulations for children for in-country implementation and adoption. For example, a standardized reporting form is available for countries to report DTG-associated adverse drug reactions, together with training materials and an adaptable data dictionary. WHO is also developing a central database for safety evaluation of DTG to enable pooling of data and inform global guidance. Countries are also being supported with the adaptation of tools, approaches and data analysis, to facilitate the implementation of adverse drug reaction monitoring in their own context.

## 4. CASE STUDIES

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Active surveillance designs typically follow standard epidemiological study designs. In epidemiology, populations are studied and the occurrence of disease is compared between exposure groups. An essential epidemiological concept is that if a drug causes disease, the drug must be administered before the disease developed and must alter the frequency of that disease. Frequency of disease can be measured by risk (cumulative incidence over a specific period) or incidence rates (number of cases for a certain number of people and a certain amount of time). The following are the key observational designs and can be applied for safety and effectiveness studies (Table 10.1).

In cohort studies, the population is divided into exposure groups and the incidence (cumulative or rate) is calculated and compared between the exposure groups. The advantage of cohort studies is that multiple outcomes can be studied at the same time. Cohort studies are usually expensive, since large populations need to be followed over time to monitor the occurrence of disease. For ARV drugs, cohorts may also be complex since treatment may change and many covariates also change over time, all of which need to be measured and considered in any analysis. As an aside, experimental studies (randomized controlled trials) have a cohort design, except that exposure does not follow real-world practice but is randomly assigned by the investigator.

An alternative to cohort studies is case-based studies, which start with the outcome (cases). In case-control studies, the past frequency of exposure to a drug in cases is compared with the frequency of exposure to the drug in controls (people without the outcome). Since the outcome is the entry point into the study and exposure needs to be assessed retrospectively, these designs are efficient but susceptible to selection and information bias, especially if they

rely on consent and self-reported exposure. The advantage is that they cost less and enable multiple exposure patterns to be studied.

In recent years, other case-based studies have been developed that are suitable for brief drug exposure or vaccine safety. They start with the cases with a specific outcome and compare exposure during case occurrence with periods of time for the same person before the case occurred (case crossover) or in unexposed periods (self-controlled case series). These studies inherently control for all confounding factors that are stable (environment and genetics) and are very cost-efficient.

Cross-sectional studies provide a snapshot at one point in time of the co-occurrence of exposure and disease and are suitable for generating hypotheses, but since the temporal association between the exposure and disease is unknown this design cannot be used to evaluate causality.

Case-based studies only provide measures of association (relative risk) between exposure and outcome (odds ratio). Cohort studies do that as well (relative risk) but also provide an absolute measure of risk or incidence.

### 4.1 Tenofovir and renal toxicity

A series of spontaneously reported cases (case series) from passive surveillance often provides the first indication of a safety signal. For example, in the mid-2000s, single case reports and case series highlighted instances of proximal renal tubular dysfunction and other renal toxicity in a few children with HIV taking tenofovir disoproxil fumarate (45,46). This led to the EMA requiring post-authorization safety studies to assess whether the recommended patient monitoring laboratory tests and evaluations are adhered to in routine care (36). Various study designs

**Table 10.1.** Examples of important pharmacovigilance issues in paediatrics and study design approaches

Pharmacovigilance issue in paediatrics	Study design	
	Optimal choices	Less optimal choices
Prenatal exposure to ART and maternal outcomes and birth defects	<p>Cohort of ART-exposed and -unexposed women and specific investigations of maternal health and birth outcomes (provides rates and associations)</p> <p>Case-control study of infants with birth defects (cases) and without (controls) (efficient design; provides a measure of association)</p>	<p>Case series of women receiving a specific ART regimen (no good reference group)</p> <p>Cross-sectional (no temporal association)</p>
Nervous system and mental effects of specific ARV drugs on children	<p>Cohort study of children initiating ARV drugs on various ART regimens (provides rates and associations)</p> <p>Case-control study of children with nervous system and mental effects (cases) and without (controls) (efficient design; provides a measure of association)</p> <p>Self-control case series (efficient design; adjust for confounders within each person)</p>	<p>Cross-sectional (no temporal association)</p>

have investigated this relationship between exposure and outcome, such as cohort (47) and case-control designs (48), randomized trials (49) and, more recently, a systematic review (50). Together, these and other reports have highlighted clinically relevant adverse renal and bone effects of regimens containing tenofovir disoproxil fumarate among children.

## 4.2 Abacavir and hypersensitivity

Abacavir is a nucleoside reverse-transcriptase inhibitor recommended by international guidelines and available in Africa. However, there have been concerns about its toxicity, including hypersensitivity reactions, which are more likely for people with the HLA B5701 genotype. Studies of adults with HIV receiving abacavir-based ART have reported an increased risk of hypersensitivity reactions and myocardial infarction (51).

One key study investigating hypersensitivity among children taking abacavir was the Antiretroviral Research for Watoto (ARROW) trial, which investigated new ART strategies for children living with HIV in Africa and had an active surveillance component. In the main trial,

grade 3 and 4 adverse events by treatment arm were compared, suggesting good tolerability of abacavir and also lamivudine (52). Follow-up continued beyond the primary endpoint, to evaluate longer-term outcomes, including safety. In ARROW, hypersensitivity related to abacavir was found to be rare, being experienced by 0.3% of trial patients (53). This finding was later confirmed in a systematic review of the evidence from trials and observational studies (54).

## 4.3 Safety of ARV drugs among HIV-exposed and uninfected children

Although surveillance studies in low- and middle-income countries are evaluating the safety of ART in pregnancy and effects on infants at delivery (55), including in Botswana (56) and South Africa (57), these studies are not following up ART-exposed infants subsequently.

In high-income countries, the Surveillance Monitoring for ART Toxicities Study in HIV-uninfected Children Born to HIV-infected Women is a cohort study measuring the safety of exposing HIV-uninfected children born to mothers living with HIV to ART in utero, using



an active surveillance approach (58). Areas of interest include effects on metabolism and growth, the heart, the nervous system and its development, behaviour, language and hearing. A novel trigger-based design provides efficient use of study and patient resources, in which trigger thresholds dictate additional prespecified evaluations rather than randomly selecting subgroups of patients to study with detailed assessments.

Other cohorts and studies use novel data linkage designs to ascertain very long-term outcome measurements from national cancer and death registries in cohort studies of children born to mothers living with HIV. For example, in France, children born to women living with HIV are linked to the National Cancer Registry (59). Findings from France's registry cohort suggested a strong association between didanosine exposure in the first trimester and transplacental oncogenicity, which led to the avoidance of didanosine during pregnancy.



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## 5. SUMMARY

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A huge number of children globally have been exposed to ARV drugs during early life, and this trend will continue for the foreseeable future. In addition, many children living with HIV are expected to continue to need ART for lifelong HIV treatment (5,51,60). In recent years, appreciation has increased of the importance of generating safety data specific to children since they are exposed to ARV drugs throughout critical growth and development phases in addition to differing from adults in absorption, distribution, metabolism and excretion of ARV drugs and concomitantly administered drugs (61).

The poor level of evidence for adverse drug reactions among children reflects some of the challenges of conducting pharmacoepidemiological studies involving children exposed to HIV and ARV drugs. In low- and middle-income countries in particular, regulatory systems are commonly weak, with the main focus being on passive surveillance.

Issues that need to be addressed include the cost of pharmacovigilance, difficulty in attributing causality, dosing errors, the generalizability of findings, data quality, the heterogeneity of exposure and populations, loss to follow-up and multiple outcomes of interest. However, many recent developments have strengthened and improved reporting, and there is a need to further capitalize on progress by improving the regulatory framework, building capacity, focusing on active surveillance, pooling existing data and harnessing WHO technical support.

All of these aspects are important for the future, when focus is likely to be increased on the role of DTG as a priority for children, as well as two-drug regimens and long-acting formulations. These new trends demonstrate a clear need for more robust pharmacovigilance monitoring to better understand the risks and safety profile of ART for children, especially in low- and middle-income countries.

## 6. KEY CONSIDERATIONS

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- Pharmacovigilance of adverse drug reactions is key to ensuring that medicines are safe.
- Pharmacovigilance studies can range from passive surveillance, which can be relatively simple and cheap to implement, to active surveillance, which may be more costly but generates more informative results.
- Major challenges of pharmacovigilance in low- and middle-income countries include a lack of robust regulatory systems that enforce manufacturer commitments to support longer-term approaches to pharmacovigilance and competing resources and capacity challenges.
- Training opportunities are available, and WHO provides technical support to implement both passive and active surveillance approaches.
- Issues of drug safety in HIV will continue for the foreseeable future, and approaches therefore urgently need to be implemented, strengthened and scaled up.

## 7. USEFUL RESOURCES

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### WHO links

- Technical guidance for Global Fund HIV proposals: treatment – pharmacovigilance for antiretroviral drugs ([http://www.who.int/hiv/pub/toolkits/3-2-8\\_Pharmacovigilance\\_3Nov.pdf](http://www.who.int/hiv/pub/toolkits/3-2-8_Pharmacovigilance_3Nov.pdf))
- Pharmacovigilance: ensuring the safe use of medicines (<http://apps.who.int/medicinedocs/pdf/s6164e/s6164e.pdf>)
- A practical handbook on the pharmacovigilance of antiretroviral medicines ([http://www.who.int/medicines/areas/quality\\_safety/safety\\_efficacy/HIVhandbook.pdf](http://www.who.int/medicines/areas/quality_safety/safety_efficacy/HIVhandbook.pdf))
- Venter WDF, Ford N, Vitoria M, Stevens W. Diagnosis and monitoring of HIV programmes to support treatment initiation and follow up and improve programme quality. *Curr Opin HIV AIDS*. 2017;12:117–22 ([http://www.who.int/hiv/pub/journal\\_articles/diagnosis-monitoring-hiv-programmes/en](http://www.who.int/hiv/pub/journal_articles/diagnosis-monitoring-hiv-programmes/en))

### Training courses

- WHO adverse events following immunization (<https://www.who-umc.org/global-pharmacovigilance/communication-in-pharmacovigilance>)
- Uppsala Monitoring Centre education and training opportunities (<https://www.who-umc.org/education-training/education-training>)
- Uppsala Monitoring Centre internships (<https://www.who-umc.org/about-us/contact-us/career-page>)

### WHO collaborating centres

- Uppsala, Sweden: <https://www.who-umc.org>
- Accra, Ghana: [http://apps.who.int/whocc/Detail.aspx?cc\\_ref=GHA-1&cc\\_region=afro&](http://apps.who.int/whocc/Detail.aspx?cc_ref=GHA-1&cc_region=afro&)
- Utrecht, Netherlands: <http://www.pharmaceuticalpolicy.nl>
- Rabat, Morocco: <http://www.capm.ma/pv-pharmacovigilance>

### Data exchange formats

- International Epidemiology Databases to Evaluate AIDS Data Exchange Standard; <http://iedea.github.io>
- HIV Cohorts Data Exchange Protocol: <http://www.hicdep.org>

### Other links

- Eu2P programme: <https://www.eu2p.org>
- International Society for Pharmacoepidemiology Pediatric Special Interest Group: <https://www.pharmacoepi.org/communities/sigs/pediatrics>
- INDEPTH network: <http://www.indepth-network.org>

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